REMARKS

Claims 1-14 and 21-50 are in this application. Claims 1, 12, 13 and 14 have been amended. Claim 1 has been amended to include a description of Aib, Deg, Dpg, and Ac5c. Support for this amendment is found on page 4 of the specification. Claim 12 has been amended to define the composition as comprising a peptide according to Claim 1 and a pharmaceutically acceptable carrier.

Claim 13 has been amended to define the cancer as breast, colon, lung, pancreatic, oral, ovarian, stomach, prostate, laryngeal and duodenum and glioblastoma and leukemia. Support for this is found on pages 15-21 of the specification.

Claims 21-50 are claims for compositions of the peptides of Claims 2-12 and method claims for the treatment of cancer using peptides of Claims 2-12.

It is noted that according to the Advisory Action of May 5, 2003 that Claims 1-11 would be allowable if claim the amendment to Claim 1 is entered. As this amendment includes an amendment to Claim 1, applicants submit that Claims 1-11 are allowable.

Claim 12 as amended and newly added Claims 21-30 define pharmaceutical compositions comprising a peptide and a pharmaceutically acceptable carrier. Applicants submit that these claims meet the requirements of 35 USC 112, first and second paragraphs and are patentable.

Claim 13 has been amended to define a method of treatment of cancer in a mammal which comprises administering an effective amount of a peptide according to Claim 1 to the mammal in need thereof, wherein the cancer is colon, lung, prostate, stomach, laryngeal, oral, breast, duodenum, ovarian or pancreatic or leukemia or glioblastoma. Claims 31-40 also define treatment of specific types of cancers.

Applicants also respectfully disagree with the Examiner's rejection of Claims 13 and 14. Applicants submit that Claims 13 and 14 and Claims 31-51 comply with the requirements of 35 USC 112, first and second paragraphs.

It is well known to screen candidates for anticancer effect in *in vitro* systems and *in vivo* animal models. Testing of anticancer compounds is standard in the art to identify cytotoxic compounds.

It is a common and standard practice and norm for testing molecules for anticancer activity *in vitro* on human tumor cell lines. (Br J Cancer. 2001 May 18; 84(10):1289-90 (Flasks, Fibres and Flanks - Preclinical tumor models for predicting clinical antitumor activity). The authors report that in vitro activity against 6 or more lung or breast cancer cell lines does predict xenograft activty against these tumor types. In articles "Semin Oncol 1992 Dec.; 19(6):622-38 (The National Cancer Institute: cancer drug discovery and development program) and "Jpn J Antibiot 1977 Dec.;30 Suppl:35-40 (Antitumor screening procedures of the National Cancer Institute)" extensive use of human tumor cell lines for identification of potential cytotoxic drugs is described.

Examples 12, 13 and 14 describe the use of the compounds of this invention *in vitro* assays. A declaration by Dr. Rama Mukherjee in which she decribes that a peptide of SEQ ID NO:11 inhibited the growth of colon adenocarcinoma *in vivo* by 53% was submitted previously.

As shown in Example 14 of this application, the cytotoxic activity of the peptide of SEQ ID NO:11 was determined by the MTT assay in which PTC cells were exposed to different concentrations of the peptide for 48 hrs. SEQ ID NO:11 shows in vitro cytotoxicity on PTC cells at a broad dose range between 2 pg to 0.2 ug (10pM - 1uM). The pattern of cytotoxicity of SEQ ID NO.11 seen at different concentrations is typical of peptides wherein at high saturation concentrations of peptide (at 1uM in this case) there is reduced cytotoxicity.

To determine the therapeutic dose in vivo one skilled in the art would be able to follow methods known in the art. One such method is described in U.S. Patent 5,565,431which issued on October 15, 1996 wherein doses are determined based upon the cancerous state of the patient. See for example, col. 3, lines 11-44. The exact *in vivo* doses are decided based on the *in vitro* cytotoxicity, general toxicity and bio-pharmaceutical properties like metabolism, protein binding.

elimination half-life etc. (Sugiyama Y & Hanano M. Pharm. Res. 1989, 6, 194-204; Sugiyama etal. J. Controlled release 1990, 13, 157-174).

The *in vivo* anti-tumor activity of SEQ ID NO.11 was tested in the PTC tumor xenograft model wherein 1.5 * 107 cells are exposed daily to therapeutic concentrations *in vivo*. Cell culture experiments show that 104 PTC cells are killed by daily dosage of 2 pg to 0.2 ug of SEQ ID NO.11. In the mouse experiments, 15 million cells were injected, which is 1500 times greater, and in theory should require daily doses of 3 ng to 300 ug to get a similar effect. But *in vitro* and *in vivo* systems cannot be compared in strict sense. Therefore, 8.5 ug daily dosage split in to two doses of 4.25 ug each was used which falls well within the therapeutically effective range and does not cause any toxicity and takes in to consideration the bio-pharmaceutical properties of the peptide as stated earlier.

In humans, based on the findings from cell culture and mouse experiments, an effective amount of the peptide can be decided by the physician depending upon the cancerous state of the patient, the peptide can be administered intravenously or by direct perfusion or other suitable means of contacting the cancer cells.

As regards the determination of a starting dose in humans from animal data, much has been published in literature on the methods followed for determination of starting human dose and for one skilled in the art this should pose least of any problems. Attached are a number of references available which provide allometric conversions of animal to human dosages.

First-time-in-human dose selection: Allometric thoughts and perspectives, by Boxenbaum and Dilea, J.Clin.Pharmacol. 35:957-966(1995). (Some of the many factors that influence dose selection in first-time-in-human studies include animal toxicology, toxicokinetics, allometric scaling, pharmokinetics, body surface area correlations and integration of preclinical pharmacologic and toxicologic data. With our present state of knowledge, we cannot provide a realistic and reasonable algorithm for ascertaining first-time-in-human doses: any decision tree would be too unwieldy.)

* Dosage Regimen Design for Pharmaceutical Studies Conducted in Animals,

J.Mordenti. J. Pharm. Sci., 75:852-57, 1986.

* Extrapolation of Toxicological and Pharmacological Data from Animals to Humans. W.Chappell & J. Mordenti, Advances in Drug Research, Vol. 20, 1-116, 1991(published by Academic Press Ltd).

Other references which is describe how to determine dosages of pharmaceutical compounds are:

* Freireich EJ et al. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey and man. Cancer Chemo Reports 1966; 50:219-244.

* Monro A. and Mordenti J. Expression of exposure in negative carcinogenticity studies: dose/body weight, dose/body surface are or plasma concentrations? Toxicolgy Pathology 1995; 23:187-98.

* Freireich E.J. et.al. Cancer Chemother. Reports 1966, 50(4) 219-244.

Based on the examples in this application, the data presented in Dr. Mukherjee's declaration and the references provided with this response, it is clear to one skilled in the art that Claims 13-14 and 31-50 are enabled.

The use of the compounds of this invention to treat the types of cancers listed in Claims 13, and 31-40 is supported in this application.

The Examiner also states that the use of the term an effective amount is indefinite. Applicants respectfully disagree. The term an effective amount is a term used in the art and is defined on page 8, lines 22-24. In addition, the application contains information on the amount of the peptides that can be used to kill tumor cells.

Applicants preserve all rights to file one or more divisional applications directed to subject matter disclosed and not currently claimed in this application.

Applicants submit that the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,

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IN THE CLAIMS

Please amend the following claims:

1. (Amended) A peptide of the formula

X-D-Phe-Gln-R1-R2-Val-R3-His-R4-NH$_2$

wherein X is acetyl or straight, branched or cyclic alkanoyl group from 3-16 carbon atoms, or X is deleted

R1 is Trp or D-Trp,

R2 is Ala, Aib or Deg,

R3 is Gly, Aib, Deg, Dpg or Ac5c,

R4 is Leu or Ile

or a hydrolyzable carboxy protecting group; wherein at least one of R2 or R3 is an α,α-dialkylated amino acid; or a pharmaceutically acceptable salt of the peptide wherein Aib is α-aminoisobutyric acid, Deg is α,α-diethyl glycine, Dpg is α,α-di-n-propyl glycine and Ac5c is 1-amino-cyclo pentane carboxylic acid.

12. (Amended) A composition comprising [an effective amount of a polypeptide] peptide according to claim 1, and a pharmaceutically acceptable carrier.

13. (Amended) A method of treatment of cancer in mammals which comprises [the administration] administering of an effective amount of a peptide according to claim 1 wherein the cancer is colon, lung, prostate, stomach, laryngeal, oral, breast, duodenum, ovarian or pancreatic or leukemia or glioblastoma.

14. (Amended) A method according to claim [11] 13, further comprising administering a chemotherapeutic compound.